Remarks

Claims 519-535, 537-555 and 557-567 are presently pending in the subject application.

Reconsideration and allowance are respectfully requested in view of the above amendments and the following remarks.

Claims 536 and 556 are canceled herein without prejudice to the prosecution of the subject matter of these claims in this or a continuing application.

Claim 519 has been amended herein to incorporate the limitation of canceled claim 536, reciting that the target nucleic acid sequence is an RNA target. Consistent with this amendment, claims 521, 522, 524, 526 and 558 have been amended herein to recite that the target nucleic acid sequence is an RNA target.

Claim 521 has been amended herein to specify that the claimed kit includes *one or more* nucleic acid polymerases and *one or more* amplification oligonucleotides.

Claims 523 and 543 have been amended herein to delete the term "about" with reference to a minimum number of modified ribonucleotides.

Claims 530 and 550 have been amended herein to indicate that unmodified forms of the first and second base regions consist of RNA and/or DNA.

Claim 537 has been amended herein to change the dependency from canceled claim 536 to claim 519.

Claim 538 has been amended herein to clarify that the probe forms a stable complex with a region of the RNA target that is folded under the nucleic acid conditions. Support for this amendment can be found in the specification at, for example, page 16, lines 11-16, and Example 12. Claim 538 has also been amended to depend from claim 519 rather than canceled claim 536.

Claim 540 has been amended herein to incorporate the limitation of canceled claim 556, thereby indicating that the amplification product is RNA.

Claims 542, 544, 546 and 548 have been amended herein to indicate that the first base region forms a complex with the amplification product in the reaction mixture.

Claim 557 has been amended herein to recite that the amplification product is formed from ribosomal RNA.

Claim 558 has been amended herein to clarify that the probe forms a stable complex with a region of the amplification product that is folded under the nucleic acid conditions. Support for this amendment is indicated above. Claim 558 has also been amended to depend from claim 540.

Claims 560 and 561 are new and depend from claims 521 and 540, respectively. New claims 560 and 561 recite that the amplification oligonucleotides and nucleic acid polymerases are sufficient to perform a transcription-based amplification reaction. Support for new claims 560 and 561 can be found in the specification at, for example, page 13, lines 24-28.

Claims 562 and 563 are new and depend from claims 538 and 558, respectively. New claims 562 and 563 recite that the claimed kit or reaction mixture does not include helper probes. Support for new claims 562 and 563 can be found in the specification at, for example, page 16, lines 11-16.

Claims 564 and 565 are new and depend from claims 538 and 558, respectively. New claims 564 and 565 recite that the probe includes at least 5 contiguous 2'-O-alkyl ribonucleotides. Support for new claims 564 and 565 can be found in the specification at, for example, page 16, lines 11-16.

Claims 566 and 567 are new and depend from claims 538 and 558, respectively. New claim 566 recites that the RNA target of claim 538 is ribosomal RNA, and new claim 567 recites that the amplification product of claim 558 is formed from a ribosomal RNA. Support for new claims 566 and 567 can be found in the specification at, for example, page 13, lines 24-28.

Other amendments to the claims were made herein for the purpose of simplifying the claim language and no new matter is being introduced thereby.

Rejection Under 35 U.S.C. § 112

Claims 523, 524, 543 and 544 stand rejected by the Examiner under 35 U.S.C. § 112, second paragraph, as being indefinite. In response, claims 523 and 543 have been amended herein to delete reference to "about" in the phrase "at least about 4 ribonucleotides." Accordingly, Applicants submit that the claims are definite and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 519-559 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Tyagi *et al.* (U.S. Patent No. 5,925,517) in view of McGall *et al.* (U.S. Patent No. 6,156,501). The Examiner contends that Tyagi teaches all the limitations of the claims except the use of 2'-O-alkyl ribonucleotides, which the Examiner submits are taught by McGall. Applicants respectfully traverse this rejection for the following reasons.

Applicants first observe that this is the third occasion in which Tyagi has been raised during the examination of this application to suggest that the claims are unpatentable. *See* Office Action dated April 4, 2005, pages 6-8 (rejection withdrawn in Office Action dated August 12, 2005); and Office Action dated December 27, 2005, pages 2-4 (rejection withdrawn in Office Action dated May 17, 2006). In response to those prior rejections, Applicants argued that there was no motivation for modifying Tyagi to include 2'-O-methylated ribonucleotides, since Tyagi cautions that an affinity pair of a unitary probe should interact "sufficiently weakly that the hybridization of the target complement sequence to its target sequence is thermodynamically favored over the interaction of the affinity pair." *See* Tyagi at col. 9, lines 45-50. McGall does not differ from the previously cited prior art references in that 2'-O-methyl ribonucleotides are considered desirable for their improved binding affinity for complementary RNA sequences. *See, e.g.*, McGall at col. 8, lines 48-54. Thus, not only was the motivation lacking for including 2'-O-methyl ribonucleotides in the stem of Tyagi's hairpin probes, it could have been viewed that such modifications would render Tyagi's probes unsatisfactory for their intended purpose. *See* MPEP § 2145.X.D.

Applicants also submit that the Examiner misinterprets, mischaracterizes or improperly applies certain teachings of the cited references. For example, with regard to claims 522, 526, 542 and 546, the Examiner concludes that Tyagi teaches first and second base regions that hybridize to the target nucleic acid. While Tyagi discloses a bimolecular probe 1 having target complement sequences 2a, 2b that hybridize to a target nucleic acid, the target complement sequences 2a, 2b do

not hybridize to each other in the absence of the target nucleic acid, as would be required by the limitations of these claims. *See* Figures 1 and 2 of Tyagi; *see also* col. 9, line 55 *et seq.* of Tyagi. Tyagi does disclose arms 3, 4 that form a stem duplex 5 in the absence of a target nucleic acid, but these arms 3, 4 do not participate in hybridization to the target nucleic acid. *See* Figure 2 of Tyagi.

With regard to claims 530 and 550, the Examiner suggests that the limitations of these claims are satisfied by Tyagi's teaching that the probes may include mixtures of RNA and DNA. To avoid any confusion and to distinguish over the teachings of Tyagi, Applicants have amended claims 530 and 550 to indicate that "unmodified forms" of the first and second base regions refers to regions consisting of RNA and/or DNA as opposed to regions including 2'-O-alkyl ribonucleotides.

Claims 532 and 552 recite that the probe includes a conjugate molecule joined to the probe at a site located within the cluster of the first base region. The Examiner submits that Figures 1-3 of Tyagi shows a probe meeting this limitation. Applicants do not understood this interpretation of the figures, since Tyagi states that the label moieties 6, 7 are conjugated to the probe 1 at the 5' and 3' termini of the stem duplex 5. *See* Tyagi at column 10, lines 44-47.

The Examiner also contends that Figure 2 of Tyagi illustrates a target sequence having a double-stranded region as required by claims 538 and 558. However, Figure 2 of Tyagi does not show a probe hybridized to a double-stranded region of the target nucleic acid, as the Examiner submits, but rather a single-stranded target hybridized to the two target complement sequences 2a, 2b of the probe 1. Nevertheless, for purposes of clarity, the claims have been amended to recite that the probe forms a complex with a folded region of the RNA target or amplification product.

This last aspect of Applicants' invention is significant because it overcame a known problem in the art with probing for structured targets. As observed by Schofield *et al.* (1997) *Appl. Environ. Microbiol.* 63(3):1143-1147, secondary structure may limit access of a beacon to its target. *See*

Attachment A, Schofield reference, at page 1144, col. 2, para. 2. (rRNA was denatured by heating); page 1147, col. 1, para. 1 (membrane hybridization used to hold rRNA in a denatured state); and page 1147, col. 1, para. 2 (rRNA target and beacon were heated together and the mixture was allowed to cool overnight). Thus, the ability of the claimed probes to hybridize to structured targets provides an unexpected benefit over self-hybridized probes lacking 2'-O-alkyl ribonucleotides.

For the reasons set forth above, Applicants submit that the presently pending claims are fully patentable in view of the cited references, considered alone or combination.

Conclusion

In view of the amendments and remarks set forth herein, Applicants submit that the subject application is in condition for allowance and notice to that effect is respectfully requested.

Please charge any fees due in connection with this Request, including the excess claims fee, to Deposit Account No. 07-0835 in the name of Gen-Probe Incorporated.

Respectfully submitted,

Date: October 31, 2007

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